

# Durability of Antirestenotic Efficacy in Drug-Eluting Stents With and Without Permanent Polymer

Robert A. Byrne, MB,\* Raisuke Iijima, MD,\* Julinda Mehilli, MD,\* Susanne Pinieck, RN,\* Olga Bruskina, MD,\* Albert Schömig, MD,\*† Adnan Kastrati, MD\*

Munich, Germany

**Objectives** We sought to assess changes in antirestenotic efficacy of drug-eluting stents (DES) by restudying subjects at 2 time points after coronary stenting (6 to 8 months and 2 years) and to compare differences in time courses of late luminal loss (LLL) between 3 different DES platforms in use at our institution.

**Background** DES therapy is associated with low levels of LLL at 6 to 8 months. The temporal course of neointimal formation after this time point remains unclear.

**Methods** This prospective, observational, systematic angiographic follow-up study was conducted at 2 centers in Munich, Germany. Patients underwent stenting with permanent-polymer rapamycin-eluting stents (RES), polymer-free RES, or permanent-polymer paclitaxel-eluting stents (PES). The primary end point was *delayed* LLL (the difference in in-stent LLL between 6 to 8 months and 2 years).

**Results** Of 2,588 patients undergoing stenting, 2,030 patients (78.4%) had 6- to 8-month angiographic follow-up and were enrolled in the study. Target lesion revascularization was performed in 259 patients; these patients were not considered for further angiographic analysis. Of 1,771 remaining patients, 1,331 had available 2-year reangiographic data (75.2%). Overall mean (SD) delayed LLL was  $0.12 \pm 0.49$  mm ( $0.17 \pm 0.50$  mm,  $0.01 \pm 0.42$  mm, and  $0.13 \pm 0.50$  mm in *permanent*-polymer RES, polymer-free RES, and permanent-polymer PES groups, respectively [ $p < 0.001$ ]). In multivariate analysis, only stent type (in favor of polymer-free RES) predicted *delayed* LLL.

**Conclusions** Ongoing erosion of luminal caliber beyond 6 to 8 months after the index procedure is observed following DES implantation. Absence of permanent polymer from the DES platform seems to militate against this effect. (J Am Coll Cardiol Interv 2009;2:291–99) © 2009 by the American College of Cardiology Foundation

From the \*Deutsches Herzzentrum and †1. Medizinische Klinik rechts der Isar, Technische Universität, Munich, Germany. Funding was completely industry-independent, provided in part by the Bavarian Research Foundation (BFS-ISAR Aktenzeichen AZ: 504/02 and BFS-DES Aktenzeichen AZ: 668/05). Dr. Byrne received grant support from the Irish Board for Training in Cardiovascular Medicine, which was sponsored by A. Menarini Pharmaceuticals (Ireland). Dr. Kastrati has received lecture fees from Bristol-Myers Squibb, Cordis, Lilly, and Sanofi-Aventis. Drs. Byrne and Kastrati had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Gradual erosion of acute procedural luminal gains has long been the Achilles' heel of percutaneous coronary intervention (1). Although the evolution of elective coronary stent placement largely negated the impact of plaque prolapse, vessel recoil, and constrictive remodeling on coronary restenosis, an iatrogenic condition—neointimal hyperplasia—assumed the role of chief culprit in delayed loss of antirestenotic efficacy. The evolution of drug-eluting stents (DES), which initially appeared to have the potential to virtually eliminate this process at 6 to 8 months after intervention, has represented a very significant milestone in percutaneous coronary intervention. Widespread adoption of DES therapy has been accompanied by a surfeit of angiographic follow-up data showing well-preserved luminal gain over 6 to 8 months, even in subsets of patients with complex lesion morphology (2–4).

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#### Abbreviations and Acronyms

**BMS** = bare-metal stent(s)  
**DES** = drug-eluting stent(s)  
**LLL** = late luminal loss  
**PES** = paclitaxel-eluting stent(s)  
**RES** = rapamycin-eluting stent(s)  
**TLR** = target lesion revascularization

Since inception, however, some misgivings have remained regarding the durability of efficacy, and the dynamics of changes in luminal caliber beyond 6 to 8 months after intervention remain largely unstudied. Animal model investigation reported evidence of “catch-up restenosis” at time points beyond those seen in bare-metal stent (BMS) animal studies (5–7). Occasional clinical reports also documented experiences with delayed loss of antirestenotic efficacy (8–10). Although sequen-

tial follow-up angiographic studies described the temporal course of and peak in coronary restenosis during both the era of conventional balloon angioplasty (11,12) and BMS implantation (13–15), such an analysis remains a scientific gap in the age of DES therapy.

Against this background, the current study was designed to assess longitudinal changes in the antirestenotic efficacy of DES in a real-world setting by restudying subjects at 2 time points following coronary stenting, namely 6 to 8 months and 2 years. In addition, we sought to assess the relative changes in antirestenotic efficacy of 3 different stent platforms—permanent-polymer rapamycin-eluting stents (RES) (Cypher, Cordis Corporation, Miami Lakes, Florida), polymer-free RES (developed in the setting of the ISAR [Intracoronary Stent and Antithrombotic Research] project), and permanent-polymer paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts)—in clinical use at our institution over the same period.

## Methods

**Study population and procedural details.** This prospective, observational study included patients older than 18 years who were undergoing DES implantation at 2 German centers in Munich, Germany, between January 2003 and July 2006, due to ischemic symptoms or evidence of myocardial ischemia in the presence of  $\geq 50\%$  *de novo* stenosis located in native coronary vessels. Patients with a target lesion located in the left main stem or in a bypass graft, with in-stent restenosis or acute myocardial infarction, or with malignancies or other comorbid conditions (e.g., severe liver, renal, and pancreatic disease) with life expectancy less than 24 months or that may result in protocol noncompliance were considered ineligible for the study. The study protocol was approved by the institutional ethics committee responsible for both participating centers, the Deutsches Herzzentrum München and the Medizinische Klinik I, Klinikum rechts der Isar, Munich, Germany. All patients gave their written, informed consent for participation in the study.

The 3 treatment groups were studied concurrently. Time zero was defined as the time of initial percutaneous intervention. Patients were treated with 1 of 3 stent types: commercially available permanent-polymer RES (Cypher stent); polymer-free RES (ISAR developed); or commercially available permanent polymer PES (Taxus stent). The stent platform used in the polymer-free arm consists of a pre-mounted, sand-blasted, 316L stainless steel microporous stent. A detailed description for creating the micropores and its rationale, as well as the specifics of the coating process and the rapamycin solution used, have been reported previously (16).

An oral loading dose of 600 mg clopidogrel was administered to all patients at least 2 h before the intervention, regardless of whether the patient was taking clopidogrel before admission. Immediately after the decision to perform the intervention, patients were given first, 500 mg aspirin intravenously or orally (if they did not receive it within the prior 12 h), and second, intra-arterial or intravenous heparin or bivalirudin. Glycoprotein IIb/IIIa inhibitor usage was at the discretion of the operators. After the intervention, all patients received 200 mg/day aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge) followed by 75 mg/day for at least 6 months, and other cardiac medications according to the judgment of patient's physician (e.g., beta-blockers, angiotensin-converting enzyme inhibitors, statins).

Rehospitalization for repeat coronary angiography was scheduled at 6 to 8 months. Patients requiring revascularization of a target lesion at the 6- to 8-month reangiography were not considered for further angiographic analysis. The remaining patients were scheduled for a further follow-up coronary angiogram at 2 years after the index intervention.

Clinical follow-up was performed by either office visit or telephone call at 6 to 8 months, 12 months, and 2 years.

**Data management, end points, and definitions.** Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Centre. Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed offline in the quantitative angiographic core laboratory (ISAR Centre, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands) by 2 independent experienced operators unaware of the treatment allocation. Analysis was performed on cineangiograms recorded after the administration of intracoronary nitroglycerin using the same single worst-view projection at all times. The contrast-filled non-tapered catheter tip was used for calibration. Quantitative analysis was performed on both the “in-stent” and “in-segment” area (including the stented segment, as well as both 5-mm margins proximal and distal to the stent). Qualitative morphological lesion characteristics were characterized by standard criteria (17).

The primary end point of the study was *delayed* (or interval) in-stent late luminal loss (LLL), defined as the difference between the minimal luminal diameter at 6-to-8-month follow-up and the minimal luminal diameter at 2-year reangiography, in those patients with paired follow-up data. The secondary end points were *final* 2-year in-stent LLL for the subgroup with paired angiographic follow-up films; *composite* in-stent LLL for the entire cohort (defined as late loss of all study patients analyzed on the basis of the latest valid angiographic follow-up whether at 6 to 8 months or 2 years); *delayed* in-segment binary angiographic restenosis (defined as diameter stenosis  $\geq 50\%$  in the in-segment area at 2 years in patients not undergoing initial revascularization at 6 to 8 months); and *composite* 2-year in-segment binary angiographic restenosis (defined as binary restenosis of all study patients analyzed on the basis of the latest valid angiographic follow-up whether at 6 to 8 months or 2 years). Target lesion revascularization (TLR) was defined as any revascularization procedure involving the target lesion due to luminal renarrowing  $\geq 50\%$  in the presence of symptoms or objective signs of ischemia (as determined in advance of angiography).

**Statistical analysis.** The data is presented as mean  $\pm$  standard deviation or counts and percentages. Differences between groups in outcome variables were assessed using the chi-square test or Fisher exact test (where expected cell values were  $<5$ ) for categorical data. For continuous data, groups were compared with analysis of variance or Kruskal-Wallis rank sum test according to whether the data was normally distributed or not. All tests were 2-sided. A p value of  $<0.05$  was considered statistically significant. Logistic regression models were established to investigate independent predictors of restenosis at 6 to 8 months and at 2 years.

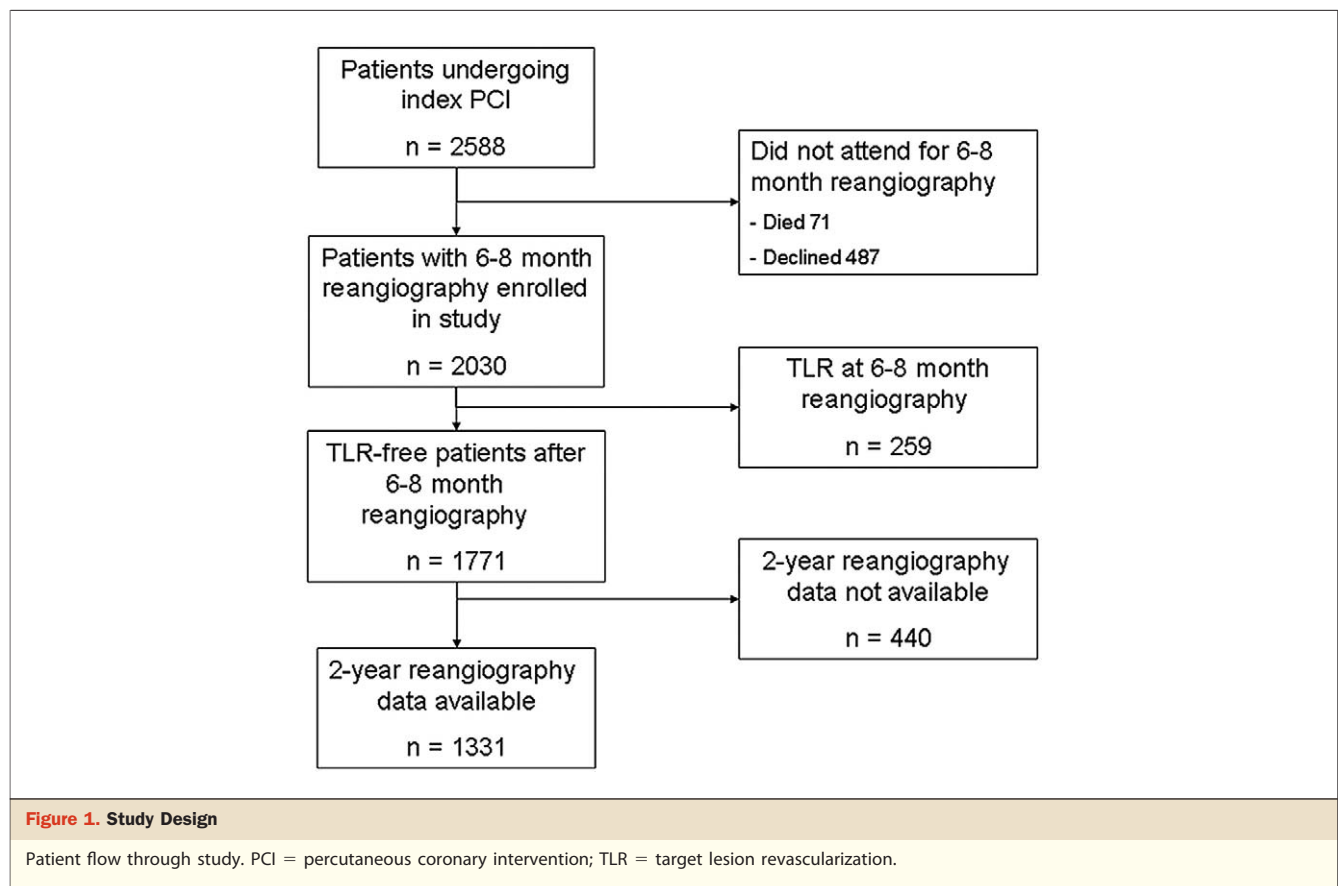
The following clinical variables were entered into the analysis model: stent group, age, gender, diabetes, hypertension, hyperlipidemia, cigarette smoker, vessel treated, complex lesion morphology, chronic occlusion, ostial lesion, bifurcational lesion, reference diameter pre-intervention, lesion length, and percentage stenosis of vessel pre-intervention.

## Results

**Baseline characteristics and procedural results.** The study patient flow chart is shown in Figure 1. Of 2,588 patients undergoing percutaneous intervention in a new coronary vessel, a total of 2,030 patients (78.4%) returned for angiographic follow-up 6 to 8 months after index stenting, had valid angiographic data, and were therefore considered eligible for enrollment in this study. Of those not returning for follow-up, 71 had died (28 [2.4%] in the permanent-polymer RES group, 13 [2.1%] in the polymer-free RES group, and 30 [3.7%] in the permanent-polymer PES group;  $p = 0.12$ ). The number of treated lesions was 2,341 (1,036 permanent-polymer RES, 565 polymer-free RES, and 740 permanent-polymer PES). Baseline clinical characteristics were similar between treatment groups (Table 1). Overall, 28.6% of patients had diabetes mellitus and 74.1% of lesions had morphology classified as B2/C according to American Heart Association/American College of Cardiology guidelines. The treatment groups were well matched in terms of lesion and procedural characteristics (Table 2).

**Angiographic outcomes at 6 to 8 months.** Angiographic outcomes are summarized in Table 3. The mean time to initial scheduled reangiography was  $200 \pm 85$  days. Overall LLL at 6 to 8 months was  $0.37 \pm 0.56$  mm—comprising a LLL of  $0.25 \pm 0.50$  mm,  $0.46 \pm 0.57$  mm, and  $0.46 \pm 0.59$  mm for permanent-polymer RES, polymer-free RES, and permanent-polymer PES, respectively ( $p < 0.001$ ). Binary angiographic restenosis was also significantly different across the 3 treatment groups: 125 (12.1%), 97 (17.2%), and 127 (17.2%) for permanent-polymer RES, polymer-free RES, and permanent-polymer PES, respectively ( $p = 0.003$ ). Restricting 6- to 8-month analysis to the subgroup of lesions that subsequently had available 2-year angiographic data ( $n = 1,580$ ), LLL for the group was  $0.26 \pm 0.42$  mm— $0.16 \pm 0.37$  mm in the patients treated with permanent-polymer RES,  $0.35 \pm 0.46$  mm in the polymer-free RES stent group, and  $0.34 \pm 0.44$  mm in the permanent-polymer PES group ( $p < 0.001$ ).

Target lesion revascularization was required in 259 patients (12.8%) at the time of 6- to 8-month reangiography and accordingly these patients were not considered for 2-year angiographic recall ( $p = 0.07$  for differences across groups). Of 1,771 remaining patients (with 2,080 lesions), valid 2-year angiographic follow-up data, and therefore paired angiographic follow-up films, were available for



1,331 (75.2%) patients (with 1,580 [76.0%] treated lesions); this rate of follow-up was similar across all 3 groups ( $p = 0.58$ ).

**Angiographic outcomes at 2 years.** Mean time to 2-year reangiography was  $699 \pm 239$  days; findings are summarized in Tables 3 and 4). With respect to the primary end

point, overall *delayed* LLL was  $0.12 \pm 0.49$  mm at 2-year angiographic follow-up— $0.17 \pm 0.50$  mm in the cohort treated with permanent-polymer RES,  $0.01 \pm 0.42$  mm in the polymer-free RES stent group, and  $0.13 \pm 0.50$  mm in the permanent-polymer PES group ( $p < 0.001$ ) (Fig. 2). With regard to secondary end points, *final* 2-year LLL in

	Overall (n = 2,030)	Permanent-Polymer RES (n = 909)	Polymer-Free RES (n = 494)	Permanent-Polymer PES (n = 627)	p Value†
Age, yrs	65.9 ± 9.8	65.7 ± 10.0	66.7 ± 9.7	65.9 ± 10.0	0.23
Male	1,858 (79.4)	718 (79.0)	391 (79.1)	500 (79.7)	0.94
Body mass index, kg/m <sup>2</sup>	27.2 ± 3.8	27.2 ± 3.9	27.3 ± 4.0	27.1 ± 3.7	0.74
Diabetes	674 (28.8)	269 (29.6)	136 (27.5)	176 (28.1)	0.67
Insulin-requiring	203 (10.0)	90 (9.9)	51 (10.3)	62 (9.9)	0.94
Hypertension	1,553 (66.3)	595 (65.5)	323 (65.4)	426 (67.9)	0.54
Current smokers	310 (13.2)	124 (13.6)	68 (13.8)	84 (13.4)	0.98
Hypercholesterolemia	1,770 (75.6)	688 (75.7)	361 (73.1)	478 (76.2)	0.43
Multivessel disease	1,975 (84.4)	769 (84.6)	408 (82.6)	528 (84.2)	0.61
Previous myocardial infarction	923 (39.4)	358 (39.4)	195 (39.5)	254 (40.5)	0.90
Prior bypass surgery	221 (9.4)	88 (9.7)	45 (9.1)	65 (10.4)	0.78
Ejection fraction,† %	55.5 ± 11.6	55.4 ± 12.1	54.9 ± 11.9	56.0 ± 11.2	0.29
Lesions/patient	1.19 ± 0.44	1.17 ± 0.43	1.20 ± 0.43	1.21 ± 0.46	0.13

Plus-minus values are mean ± SD, otherwise data are shown as n (%). †Data available for 92.4% of patients.  
PES = paclitaxel-eluting stent; RES = rapamycin-eluting stent.

**Table 2. Lesion and Procedural Characteristics**

	Overall (n = 2,341)	Permanent-Polymer RES (n = 1,036)	Polymer-Free RES (n = 565)	Permanent-Polymer PES (n = 740)	p Value
Ostial	437 (18.7)	197 (19.0)	96 (17.0)	144 (19.5)	0.49
Bifurcational	625 (26.7)	270 (26.1)	148 (26.2)	207 (28.0)	0.64
Chronic occlusion	141 (6.0)	64 (6.2)	44 (7.8)	33 (4.5)	0.04
Complex lesion (type B2/C)	1,735 (74.1)	775 (74.8)	415 (73.5)	545 (73.6)	0.79
Lesion length, mm	13.7 ± 7.5	14.1 ± 7.8	13.6 ± 6.5	13.4 ± 7.7	0.06
Reference vessel, mm	2.70 ± 0.50	2.70 ± 0.51	2.70 ± 0.49	2.71 ± 0.51	0.84
MLD, pre, mm	1.08 ± 0.48	1.07 ± 0.48	1.10 ± 0.46	1.09 ± 0.48	0.15
Stenosis, pre, %	60.1 ± 15.2	60.6 ± 15.2	59.6 ± 14.4	59.7 ± 15.9	0.13
Balloon/vessel ratio	1.14 ± 0.11	1.14 ± 0.11	1.14 ± 0.09	1.14 ± 0.11	0.97
Maximal balloon pressure, atm	14.7 ± 3.0	14.7 ± 3.0	14.5 ± 3.0	14.8 ± 2.9	0.36
MLD, post, mm	2.58 ± 0.45	2.57 ± 0.45	2.56 ± 0.44	2.61 ± 0.46	0.13
Stenosis, post, %	8.5 ± 6.3	8.7 ± 6.3	8.3 ± 5.8	8.4 ± 6.56	0.06

Plus-minus values are mean ± SD, otherwise data are shown as n (%).  
MLD = minimal luminal diameter; other abbreviations as in Table 1.

the group with paired angiographic follow-up lesions (n = 1,580) was  $0.38 \pm 0.56$  mm— $0.33 \pm 0.33$  mm for permanent-polymer RES,  $0.35 \pm 0.49$  mm for polymer-free RES, and  $0.47 \pm 0.59$  mm for permanent-polymer PES;  $p < 0.001$  (Fig. 3).

In terms of *composite* 2-year LLL, the figure for the overall group (n = 2,341 lesions) was  $0.45 \pm 0.62$  mm—representing  $0.37 \pm 0.60$  mm for permanent-polymer RES,  $0.47 \pm 0.59$  mm for polymer-free RES, and  $0.55 \pm 0.66$  mm for permanent-polymer PES ( $p < 0.001$ ). There were

also significant differences between the stent groups in the incidence of *delayed* binary angiographic restenosis (92 [13.1%] for permanent-polymer RES, 27 [7.2%] for polymer-free RES, and 75 [15.0%] for permanent-polymer PES;  $p = 0.002$ ) (Fig. 3) and overall 2-year *composite* binary angiographic restenosis (179 [17.3%] for permanent-polymer RES, 94 [16.6%] for polymer-free RES, and 161 [21.8%] for permanent-polymer PES;  $p = 0.02$ ).

Among 109 lesions with binary restenosis at 6 to 8 months that did not undergo TLR, 63 were restenosis-free

**Table 3. Results of 6- to 8-Month and 2-Year Reangiography by Stent Type**

	Overall	Permanent-Polymer RES	Polymer-Free RES	Permanent-Polymer PES	p Value
6- to 8-month reangiography					
Reangiography interval, days	200 ± 85	203 ± 88	197 ± 74	199 ± 88	0.14
Lesions analyzed	2,341	1,036	565	740	
MLD, in-stent, mm	2.21 ± 0.69	2.31 ± 0.65	2.09 ± 0.72	2.15 ± 0.72	<0.001
Stenosis, in-stent, %	22.3 ± 20.0	19.1 ± 18.1	24.8 ± 21.4	24.5 ± 20.8	<0.001
Late loss, in-stent, mm	0.37 ± 0.56	0.25 ± 0.50	0.46 ± 0.57	0.46 ± 0.59	<0.001
MLD, in-segment, mm	1.94 ± 0.65	2.01 ± 0.63	1.86 ± 0.66	1.91 ± 0.67	<0.001
Stenosis, in-segment, %	32.0 ± 18.1	30.2 ± 17.0	33.4 ± 18.9	33.4 ± 18.7	<0.001
Binary restenosis, in-segment	349 (14.9)	125 (12.1)	97 (17.2)	127 (17.2)	0.003
2-year reangiography					
Reangiography interval, days	699 ± 239	701 ± 251	695 ± 237	700 ± 222	0.77
Lesions analyzed	1,580	704	375	501	
MLD, in-stent, mm	2.20 ± 0.67	2.24 ± 0.67	2.21 ± 0.64	2.15 ± 0.69	0.015
Stenosis, in-stent, %	22.5 ± 18.9	21.9 ± 18.6	20.5 ± 18.1	24.7 ± 19.8	<0.001
Delayed late loss, in-stent, mm	0.12 ± 0.49	0.17 ± 0.50	0.01 ± 0.42	0.13 ± 0.50	<0.001
Composite late loss, in-stent, mm	0.45 ± 0.62	0.37 ± 0.60	0.47 ± 0.59	0.55 ± 0.66	<0.001
MLD, in-segment, mm	1.94 ± 0.63	1.95 ± 0.63	1.96 ± 0.60	1.90 ± 0.65	0.19
Stenosis, in-segment, %	32.1 ± 17.3	32.3 ± 17.1	29.7 ± 16.4	33.5 ± 18.1	0.004
Delayed binary restenosis, in-segment	194 (12.2)	92 (13.1)	27 (7.2)	75 (15.0)	0.002
Composite binary restenosis, in-segment	434 (18.5)	179 (17.3)	94 (16.6)	161 (21.8)	0.02

Plus-minus values are mean ± SD, otherwise data are shown as n (%).  
Abbreviations as in Tables 1 and 2.



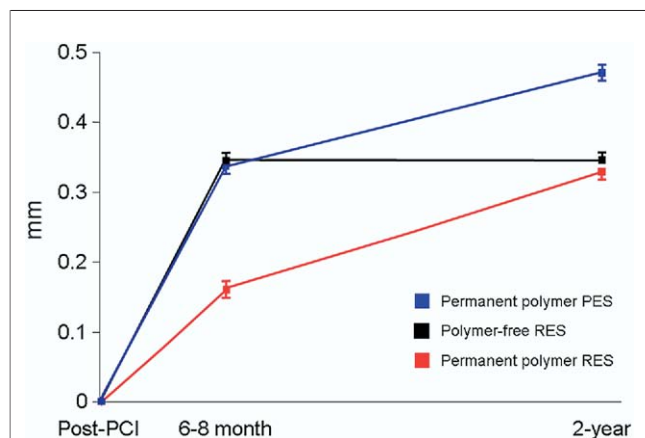
**Table 4. Overall Results of 6- to 8-Month and 2-Year Reangiography**

	Pre-Procedure	Post-Procedure	6 to 8 Months	2 Years
Lesions with 6- to 8-month follow-up (n = 2,341)				
MLD, in-stent, mm	1.07 ± 0.48	2.57 ± 0.45	2.21 ± 0.69	
Late loss, in-stent, mm			0.37 ± 0.56	
Lesions with 2-year follow-up (n = 1,580)				
MLD, in-stent, mm	1.09 ± 0.47	2.58 ± 0.46	2.32 ± 0.58	2.20 ± 0.67
Late loss, in-stent, mm			0.26 ± 0.42	0.38 ± 0.62
Plus-minus values are mean ± SD. Abbreviations as in Table 2.				

at 2 years. Conversely, of 1,471 nonrestenotic lesions at 6 to 8 months, 148 met criteria for binary angiographic restenosis at 2 years with a significant difference in likelihood of progression in favor of those lesions treated with the polymer-free RES (76 [11.4%] with permanent-polymer RES, 14 [4.1%] with polymer-free RES, and 58 [12.6%] with permanent-polymer PES;  $p < 0.001$ ).

**Multivariate analysis.** Predictors of LLL at 6- to 8-month reangiography were stent group (favoring permanent-polymer RES), patient age, complex lesion morphology, chronic occlusion, ostial lesion location, and lesion length. Only stent type (in favor of polymer-free RES) remained a predictor of *delayed* LLL between 6 to 8 months and 2 years (Table 5). In terms of binary angiographic restenosis, stent group (favoring permanent-polymer RES), hypertension, complex lesion morphology, chronic occlusion, and pre-procedure reference diameter predicted 6- to 8-month restenosis while stent type (in favor of polymer-free RES), diabetes, chronic occlusion, ostial lesion location, and pre-procedure reference diameter predicted later *delayed* restenosis.

**Clinical outcomes.** During the 6 to 8 months following index percutaneous coronary intervention, 259 patients



**Figure 2. Primary End Point: LLL**

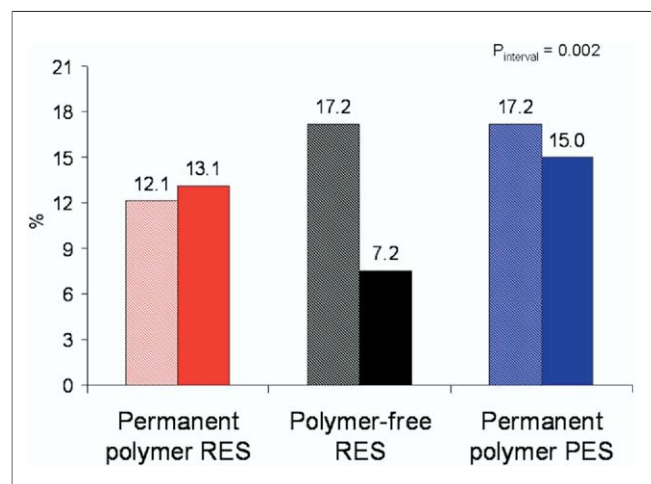
Data are displayed as mean ± standard error of mean. LLL = late luminal loss; PES = paclitaxel-eluting stent; RES = rapamycin-eluting stent.

(12.8%) underwent TLR (99 [10.9%] in the permanent-polymer RES group, 73 [14.8%] in the polymer-free RES group, and 87 [13.9%] in the permanent-polymer PES group;  $p = 0.07$ ). At 2 years, TLR had been performed in 408 (20.1%) patients (171 [18.8%], 86 [17.4%], and 151 [24.1%] in permanent-polymer RES, polymer-free RES, and permanent polymer PES groups, respectively;  $p = 0.009$ ).

At 2-year follow-up, 77 of 2,030 enrolled patients had died (3.8%). Differences in 2-year mortality across the treatment groups were of borderline significance (30 [3.3%], 14 [2.8%], and 33 [5.3%] in permanent-polymer RES, polymer-free RES, and permanent-polymer PES groups, respectively;  $p = 0.06$ ).

## Discussion

In this large-scale, 2-center prospective systematic angiographic follow-up study, we found that ongoing reduction in luminal caliber beyond 6 to 8 months after index stenting



**Figure 3. Secondary End Point: Binary Angiographic Restenosis**

**Shaded bars** represent restenosis at 6 to 8 months. **Full-color bars** represent delayed (interval) restenosis at 2 years in patients who did not undergo revascularization at 6 to 8 months.  $p_{\text{interval}}$  represents  $p$  value for differences in interval progression between 6 to 8 months and 2 years. Abbreviations as in Figure 2.

**Table 5. Multivariate Predictors of LLL at 6- to 8-Month and 2-Year Reangiography**

	Late Loss at 6 to 8 Months	Late Loss at 2 Years
Stent group	<0.001*	<0.001†
Age	<0.001	
Diabetes		0.05
Complex lesion (B2/C)	<0.001	
Chronic occlusion	<0.001	
Ostial lesion	<0.001	
Lesion length	<0.001	

\*Permanent-polymer RES stent superior. †Polymer-free RES stent superior.  
LLL = late luminal loss; other abbreviations as in Table 1.

procedure is a feature of DES therapy and that there appears to exist a device specificity in this delayed attenuation of antirestenotic efficacy in favor of a platform devoid of permanent polymer. These findings lend support to the hypothesis of a possible late “catch-up” restenosis, predicated to a large extent on observations in earlier animal models and anecdotal clinical experience (5–7,9,10,18,19). In those patients with paired 6- to 8-month and 2-year angiographic follow-up results, overall 2-year LLL was  $0.38 \pm 0.56$  mm. This comprised a *delayed* LLL of  $0.12 \pm 0.49$  mm over and above  $0.26 \pm 0.42$  mm observed at initial reangiography. These observations are in marked contrast to findings from studies with late angiographic follow-up in the era of BMS, which revealed a peak in BMS restenosis at 6 months in human subjects (13–15). Thereafter, volumes of restenotic plaque tend to remain stable or indeed regress, at least over the medium term (up to 4 years) (20), most likely due to completion of vessel wall healing in association with a degree of positive remodeling, and consequently a stabilization or modest increase in luminal caliber. As restenosis tended to have “declared itself” at 6 to 9 months after intervention, this time window was historically considered appropriate for angiographic restudy and continued to be thought of as such into the era of DES.

Intuitively, the time course of restenosis in the DES era might be considered quite different. In addition to the findings from animal studies, numerous reports in DES-treated human subjects have documented ongoing vessel wall inflammation and failure of re-endothelialization in subjects in excess of 12 months after coronary stenting (9,21–24). A very convincing body of experimental and clinical evidence implicates such inflammation as the primary driver of restenosis via the vehicle of neointimal hyperplasia (25). As intravascular ultrasonic follow-up was beyond the scope of this current analysis, we are unable to confirm that the observed “late luminal creep” is definitively due to neointimal hyperplasia, although any other mechanism seems highly unlikely. The prime suspect for this persistent inflammatory response in DES-treated patients seems to be residual permanent polymer that results in

persisting proinflammatory and thrombogenic effects and may present a spectrum of clinical syndromes, ranging from systemic hypersensitivity reactions, through late stent thrombosis and late malapposition, to late-onset in-stent restenosis. In addition, failure of stent endothelialization in itself clearly presents a nidus for platelet activation and fibrin deposition, which may initiate the chemokine cascade leading to neointimal hyperplasia, quite independent of the presence of permanent polymer.

To date, the magnitude of the problem due to late neointimal growth consequent on ongoing vessel wall inflammation remains largely unstudied. Clinical and pathological case reports and adverse event series are by their nature anecdotal. Few studies have reported long-term invasive follow-up in DES-treated patients in a systematic fashion. What limited data exists is typically based on extended follow-up of patients treated with DES implantation early in the DES era and involves relatively simple lesion subsets. Aoki et al. (26) reported the results of 2-year intravascular ultrasound analysis in 161 patients treated with slow- or moderate-release permanent-polymer PES or with BMS. They found that whereas BMS-treated patients showed a compaction of the neointima between 6 months and 2 years, the DES-treated groups exhibited an increase in neointimal volume albeit without evidence of a loss of luminal caliber. Park et al. (27) reported 2-year invasive follow-up on 53 patients treated with an experimental polymer-free PES and surprisingly noted a catch-up phenomenon restricted to a subgroup treated with a higher-dose-PES. Even though Sousa et al. (28) report angiographic follow-up as far out as 4 years after implantation of early model RES, their results similarly lack general applicability due to the low number of patients studied ( $n = 30$ ) and the inclusion of only simple coronary lesions.

Although reports of a maintained clinical superiority of DES over BMS out to 4 years (as far as TLR is concerned) are reassuring (29–32), the implications of our data may have particular relevance as regards the conduct of future trials comparing different stent platforms and the choice of the most appropriate time point for protocol-mandated angiographic follow-up. As concerns regarding increasingly large sample sizes (in superiority comparison trials) and efficacy drift (in studies with a noninferiority design) come to the fore, there is an accumulating evidence base on the validity of angiographic surrogates of clinical device efficacy in DES trials (33–36). Furthermore, the influence of protocol-mandated follow-up reangiography on rates of TLR has also prompted the suggestion that protocol angiography be standardized at 13 months after index percutaneous coronary intervention—a time point beyond that of primary 12-month clinical end point assessment (37). However, as the time point at which restenotic plaque volume in DES might be expected to peak remains unknown and as LLL and binary restenosis appear to be dynamic ongoing

processes between 6 to 8 months and 2 years, perhaps caution is necessary in the interpretation of interdevice efficacy comparisons based solely on angiographic follow-up at this proposed time point.

Importantly, we observed that interval LLL in this current analysis was a phenomenon restricted only to permanent-polymer-based stents—no appreciable interval loss was seen with the polymer-free RES platform. In actual fact, a multivariate analysis model showed that the only predictor of interval LLL was stent type (in favor of the polymer-free RES platform). Although differences between DES platform performances may be due to any of its primary components—namely stent backbone, active drug, or type of polymer—absence of permanent polymer is the distinguishing feature of the polymer-free RES in this current comparison. These observed differences in interval LLL may represent the first evidence that the absence of permanent polymer from the coronary milieu over the mid- to long-term may translate into an improved late antirestenotic efficacy, in addition to the attractive proposition of an enhanced safety profile in the context of the risk of late stent thrombosis. In this regard, though we previously demonstrated superior and equivalent efficacy of the polymer-free RES platform against BMS (16) and Taxus (38), respectively, the limitations of the drug release kinetics inherent to a platform devoid of drug polymer resulted in an antirestenotic efficacy inferior to that of the Cypher stent, when this was used as comparator (39). Encouraging clinical results with novel DES using biodegradable polymers have been published recently. These platforms show equivalent angiographic and clinical outcomes to Cypher at 9 to 12 months, and as they theoretically become equivalent to a polymer-free platform at 6 to 8 weeks, the potential of maintained low levels of LLL out to 2 years is an interesting prospect (39,40).

**Study limitations.** This study was designed to assess changes in antirestenotic efficacy of DES over a 2-year time period following stent implantation. Inherent in the analysis of our primary end point was the exclusion of patients requiring revascularization at initial 6- to 8-month follow-up as at this point, time zero was considered to be reset. The influence of survival bias is unavoidable. Questions pertaining to clinical outcomes or device safety (including late stent thrombosis) are not specifically addressed in this paper. Intergroup comparison between cohorts treated with different stent platforms are limited by the nonrandomized nature of our investigation. Among patients with restenosis who did not undergo TLR and were subsequently restenosis-free at 2 years, while neointimal contraction is 1 possible explanation, the margin of error associated with quantitative coronary angiography analysis may also have contributed.

The choice of any specific time point after the index stenting procedure as the point for late reangiography may be regarded as somewhat arbitrary given the lack of evidence

as to when restenotic plaque volume may be expected to peak. Although we acknowledge that direct imaging of the coronary vessel wall may strengthen the assertion that ongoing reduction in luminal caliber is definitively due to neointimal hyperplasia, any other mechanism seems highly unlikely.

## Conclusions

We have demonstrated that ongoing LLL beyond 6 to 8 months after the index procedure is observed following DES implantation. Absence of permanent polymer from the DES platform seems to militate against this late reduction in antirestenotic efficacy. These findings may have implications regarding the time point of efficacy assessment in future DES trials and the role of permanent polymer in future DES designs.

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**Reprint requests and correspondence:** Dr. Robert A. Byrne, ISAR Centre, Deutsches Herzzentrum München, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: [byrne@dhm.mhn.de](mailto:byrne@dhm.mhn.de).

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**Key Words:** coronary restenosis ■ stents/adverse effects ■ follow-up studies ■ cell proliferation/drug effects ■ immunosuppressive agents/therapeutic uses ■ polymers ■ 2-year reangiography.